TUBERCULOSIS TRIALS CONSORTIUM

(TBTC)

BY-LAWS

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Introduction

The United States Public Health Service (USPHS) and the Veterans Administration (VA) have a distinguished history of conduct of clinical trials to evaluate new drug regimens for both the treatment and prevention of tuberculosis. In 1960, the Centers for Disease Control and Prevention (CDC) assumed a major role in these studies when the USPHS Tuberculosis Division was transferred to CDC. Subsequently, CDC coordinated a series of multi-center clinical trials which helped to establish rifampin-based, short-course therapy as the standard for tuberculosis treatment in the U.S. It also conducted studies to provide the scientific basis for preventive chemotherapy, which remains a major component of the CDC tuberculosis elimination strategy.

Currently new drugs and regimens for both tuberculosis treatment and prevention, new diagnostic tests, and new vaccine candidates are becoming available for clinical investigation. Concurrently, the challenges posed by the goal of TB elimination are increasing, as rates of drug resistance increase and as the costs associated with assuring high rates of adherence rise.

In 1993, the CDC established the Tuberculosis Trials Consortium (TBTC) for the purpose of conducting clinical trials of new drugs and regimens for the treatment and prevention of tuberculosis. The TBTC is comprised of clinical investigators from academic medical centers, health departments, and Veterans Administration (VA) medical centers, working closely with staff from the CDC's Division of Tuberculosis Elimination (DTBE). With the successful undertaking of USPHS Study 22 (the Rifapentine Clinical Trial), the consortium is functioning efficiently and provides a unique and important resource for further clinical studies.

1. TBTC Mission

The mission of the TBTC is to conduct programmatically relevant clinical, laboratory and epidemiologic research concerning the diagnosis, clinical management, and prevention of tuberculosis infection and disease.

2. Purpose

Conduct research that expands clinical and epidemiologic knowledge of tuberculosis and facilitates the diagnosis, clinical management, and prevention of tuberculosis infection and disease.

Integrate research into the care of persons with tuberculosis infection and disease.

Develop research questions that are relevant to program settings in general.

Promote research within local tuberculosis control programs through collaboration and collaboration on clinical research of relevance to public health settings.

Provide a forum for international collaborative research of importance to both domestic and international tuberculosis control.

3. General Principles

The TBTC will perform research on tuberculosis issues of clinical and public health interest. This may include but will not be limited to clinical, preventive, epidemiologic, diagnostic, prognostic, cost-benefit, operational and vaccine studies. All studies will be performed with careful attention to scientific validity and relevance to tuberculosis control programs in both the developed and the developing world.

The investigators will be careful stewards of the funds entrusted to them for this research, endeavoring to provide the most useful knowledge at a reasonable cost and being committed to continuous improvement in the quality of research performed.

The TBTC will be governed by the TBTC Steering Committee, with all major decisions reached by a majority vote of the steering committee, except where specifically noted to be by a two-thirds majority. CDC DTBE will share responsibility and authority for these decisions with the Steering Committee through its representation on the Steering Committee and subcommittees and in its role in funding TBTC investigations. CDC will also provide oversight and concurrence through the DTBE Scientific Advisory Group.

All scientific activities of the TBTC will be performed in a spirit of open communication and mutual respect. In addition to providing knowledge that will increase the ability to control TB, the TBTC will seek to develop and maintain clinical and investigative skills in persons working in TB investigation, care and control. All activities of the TBTC will be guided by the knowledge that participation in the TBTC is an important manifestation of public service and these activities must be of the highest integrity, justifying the public trust that accompanies this responsibility.

4. Roles and Responsibilities of DTBE and TBTC

CDC is the funding agency for the TBTC and bears ultimate fiscal, regulatory, and scientific accountability for all TBTC activities. DTBE will communicate DTBE priorities and perspectives to the TBTC Steering Committee. The TBTC will maintain an accountable governance process that shares decision-making between the TBTC and DTBE concerning the science and management of the TBTC.

The following is a list of DTBE responsibilities.

DTBE will promote its scientific research agenda by:

Providing broad framework of DTBE research priorities and the role of TBTC research, particularly as it relates to other DTBE-sponsored research;

Communicating in a timely manner any substantive changes in DTBE priorities or plans for the TBTC; and

Serving as an information resource on activities related to TBTC research and functioning.

DTBE will provide support and direction by:

Providing resources to support TBTC research and related activities, as well as appropriate scientific and operational support for development of the TBTC scientific agenda and for specific protocols;

Providing review and final approval of all TBTC research;

Providing review and approval of TBTC Steering Committee decisions based on merits, scientific mission, and priorities of DTBE;

Managing the overall TBTC budget issues; and

Facilitating meetings between the TBTC and DTBE staff to review the research priorities to ensure development of studies that contribute to the overall research agenda of DTBE.

DTBE will ensure the quality of TBTC research by:

Ensuring that all activities are conducted in accordance with appropriate Federal regulations and provide contract management guidance;

Participating in performance assessment of the TBTC using mutually agreed upon performance standards; and

Ensuring that the TBTC meets the performance standards described in the contracts with each TBTC unit and the responsibilities listed below by adjustment of funding, withholding of support, or suspension or termination of the award;

The following is a list of TBTC responsibilities.

The TBTC will develop its program of research by:

Meeting with DTBE staff to review DTBE priorities; and

Developing a research agenda consistent with the mission of the TBTC and priorities of DTBE.

The TBTC will conduct high quality research by:

Developing specific protocols that address appropriate scientific questions consistent with the scientific mission of the TBTC;

Initiating, conducting, and concluding individual studies in exemplary fashion (i.e., ensuring studies can be completed given current capacity, collecting accurate data, following patients for the length of the study, monitoring the status of ongoing studies);

Initiating and implementing an education/training program that supports the TBTC investigators' conduct of scientifically sound research; and

Disseminating interim and final results of research in a prompt fashion and use an equitable process for authorship, presentation and recognition with full and appropriate involvement of TBTC and DTBE staff;

The TBTC will provide oversight and quality assurance for its research by:

Initiating and implementing quality control procedures that meet mutually agreed upon standards, and take corrective actions when necessary;

Initiating and implementing a performance evaluation procedure that meets mutually agreed upon standards;

Conducting research in accordance with Federal regulations and coordinate with DTBE staff on scientific decisions; and

Submitting required fiscal and performance reports from each unit to DTBE.

5. Structure and Function

Steering Committee

The Steering Committee serves as the central decision making body for the TBTC.

Functions of the TBTC Steering Committee

Develop a long-term comprehensive scientific agenda for the TBTC with the assistance of the Core Science Group and the DTBE Scientific Advisory Group; and

Ensure consistency with the overall TBTC mission and the research priorities of DTBE;

Review and update the overall TBTC scientific agenda on an ongoing basis.

Maintain overall responsibility for development of TBTC scientific studies:

Receive updates from the Core Science Group on status of new research ideas;

Approve/disapprove concepts for protocol development;

Make decisions on initiation of protocols taking capacity, priority, feasibility in terms of staffing and cost, and status of ongoing research into account;

Oversee the work of the Executive Committees (Core Science Group, Implementation and Quality Committee, Publications and Presentations Committee, and Advocacy and External Relations Committee)

Receive recommendations from them

Make decisions based on these recommendations

Ensure equitable membership on Executive Committees and protocol teams and provide arbitration if problems occur

Approve any recommended changes in executive committee missions and functions

Evaluate the progress of ongoing protocols with the assistance of the Implementation and Quality Committee (IQC);

Review accrual data provided by IQC

Assure timely completion of protocols

Enforce quality standards recommended by IQC for protocols

Make decisions on continuation or termination of protocols, based on recommendations from the Executive Committees and protocol teams

Review in an ongoing manner the mission of the TBTC and the priorities of DTBE and ensure that the operations of the TBTC are consistent with these;

Appoint members to Working Groups and Task Forces of the Steering Committee, as necessary.

Steering Committee Membership

Voting members of the Steering Committee include:

One representative from each TBTC unit
One DTBE representative

Non-voting members of the Steering Committee include:

One Monitoring Center representative
Chairs of the Executive Committees (unless they also represent a TBTC unit)
The Executive Coordinator of the Steering Committee

The Steering Committee will have a chair and co-chair. The chair will be a member of the Steering Committee from one of the TBTC sites, elected by at least a two-thirds majority. The co-chair will be the DTBE representative who will be appointed by the DTBE Scientific Advisory Group.

Terms of Office

The term of office for the chair and co-chair will be 2 years for each position. The chair will be chosen through a process of nominations from the field, followed by a vote of the Steering Committee, with runoff votes as necessary to achieve a two-thirds majority.

The Chair and Co-Chair may be re-elected/appointed.

The chair will perform the following functions:

Organize and chair Steering Committee meetings;

Meet with key DTBE personnel on a regular basis, provide a liaison between DTBE and the Steering Committee, and be a spokesperson for the TBTC with DTBE;

Provide a liaison between the TBTC and other research organizations and government agencies;

Represent the TBTC as required; and

Provide oversight of the Executive Committees.

The co-chair will:

Serve as chair when chairperson is unable to do so;

Collaborate with the chair to assure that Steering Committee responsibilities are being met;

Provide a liaison to the Executive Committees from the Steering Committee;

Attend meetings, and chair meetings in the absence of the chair.

Executive Coordinator of the Steering Committee

The chair will be supported by an Executive Coordinator from DTBE.

The Executive Coordinator will:

Provide a contact point for DTBE, the Administrative Group, and others;

Assist the chair to plan meetings, contact individuals, plan agendas, track the work of the Steering Committee, etc.;

Serve as liaison from the chair to the Executive Committees through participation in conference calls and face-to-face meetings to gather information for the chair and to provide information from the chair to the conference call/meeting participants.

Steering Committee Meetings

The Steering Committee convenes during periodic conference calls, at each national TBTC group meeting, and at other times as deemed necessary by the Steering Committee. The following rules will govern Steering Committee meetings:

The Steering Committee chair, or in his/her absence the co-chair, will oversee the meeting.

Robert's Rules of Order will be used to govern meetings; each chair/co-chair will be provided with a summary of these rules. Variances may be approved by a simple majority vote.

Steering Committee meetings will be open to all TBTC members and DTBE staff, but it is expected that most of the discussion of issues will be by members of the committee.

Prior to voting, the chair will ask members to state their views. It is expected that input from nonmembers of the Steering Committee will be primarily through participation on Executive Committees.

Issues voted on by the Steering Committee will be decided by a simple majority (50% plus 1). The two exceptions are:

A two-thirds majority of the voting membership of the Steering Committee will be required to start or stop TBTC studies.

A two-thirds majority of the voting membership of the Steering Committee will be required to change the TBTC By-Laws.

Succinct minutes will be taken of each meeting and circulated to all members of the committee, chairs of the executive committees and administrative group in a timely manner (within 14 days).

If a Steering Committee member is unable to attend a meeting, he/she may appoint an alternate to attend the meeting and vote his/her proxy.

Executive Committees

Four Executive Committees will be established by the Steering Committee. The executive committees report to, and are accountable to, the Steering Committee. Each Committee has a specific mission that is an integral part of the function of the entire TBTC, and these functions will be coordinated by the Steering Committee, eliminating duplication of effort. Each committee is aware of the current tasks for the others through the chairs' attendance as nonvoting members at Steering Committee meetings and receipt of distributions of information to Steering Committee members, e.g., e-mail and written communications.

Following is a list of TBTC Executive Committees:

Core Science Group
Implementation and Quality Committee
Publications and Presentation Committee
Advocacy and External Relations Committee

The Executive Committees will convene via regularly scheduled conference calls and periodically during face-to-face meetings at national TBTC group meetings.

Recommendations from the Executive Committees will be presented to the Steering Committee during periodic conference calls and face-to-face meetings. The recommendations will be discussed and voted upon by the Executive Committee prior to presentation to the Steering Committee.

Executive Committees may create Working Groups to focus on specific functions and short-term Task Forces to deal with specific tasks. Both of these will report back to the parent Committee with recommendations for action.

Terms of membership and office shall be for 2 years on a rotating basis. If a vacancy opens within one year of initial appointment, the position will be filled at the next TBTC Group meeting. If a vacancy opens one year or more after initial appointment, the position will not be filled until the next election cycle unless the Steering Committee determines that the position should be filled earlier.

Election Process and Functions of the Executive Committee Chair/Co-Chair

The chair and co-chair of each executive committee will be nominated and elected by the members of that committee.

The chair will be nominated and elected first, followed by nomination and election of the co-chair.

The term of office will be 2 years for the chair and co-chair

An individual may not be chair/co-chair of more than one Committee.

The co-chair will not automatically succeed the chair.

The chair of each executive committee will attend Steering Committee meetings as a nonvoting member and will report on the activities of the committee that he/she chairs. The chair of each Executive Committee may also represent his/her unit on the Steering Committee.

Core Science Group

Mission: To develop research related to the diagnosis, treatment and prevention of tuberculosis and to recommend research to the Steering Committee for approval and further development.

The Core Science Group will:

Identify scientific opportunities, gaps in current knowledge, and research questions relevant to the diagnosis, treatment and prevention of tuberculosis;

Review the literature and confer with other research organizations;

Coordinate research information within the TBTC:

Gather and disseminate information about various diagnostic tests, new drugs and other therapeutic interventions, including new methods to prevent tuberculosis in infected persons, and new vaccines;

Accelerate publication of results of TBTC studies

Guide the development of TBTC research:

Receive research ideas developed by TBTC members and/or generate research ideas that are consistent with the overall TBTC scientific agenda;

Prioritize research ideas and determine which should be developed into concepts (see TBTC concept/protocol development process for details - to be developed);

Report to the Steering Committee the status of research ideas reviewed and the rationale for decisions made;

Develop study concepts, and following review by Steering Committee, designate protocol team chairs and protocol team members for the development of concepts into full protocols, including protocol-specific consent and case report forms;

Review protocols and recommend to the Steering Committee whether or not implementation should take place.

Membership of the Core Science Group

A group of nine voting members will be responsible for carrying out the mission and functions of the Core Science Group. Any TBTC member can apply for membership, and the Steering Committee will choose 8 representatives from the slate of applicants who have submitted a short biography and a statement of past and potential contributions to the science of the TBTC. The other voting member will be a DTBE staff member appointed by the Co-Chair of the Steering Committee.

Non-voting members will include 1 representative each from the Data Center and the Implementation and Quality Committee. (The representative of DTBE and of the Data Center may be the same person).

The CSG will set a standard for participation and report the standard to the Steering Committee. The CSG chair may request that a member who is not meeting the standard for participation resign from the committee and may request that a replacement be chosen either by special election or by special appointment.

A chair and co-chair of the CSG will be chosen by majority vote of the members.

Terms of office for the CSG members will be 2 years, and the terms will be staggered so that four members are elected one year and four the next year. Members may be re-elected.

<u>Implementation and Quality Committee (IQC)</u>

Mission: To ensure that plans for implementing TBTC protocols are appropriate and feasible and to assure that research performance and data quality within the TBTC are of the highest possible quality

IQC will:

Ensure that plans for implementing TBTC protocols are appropriate and feasible:

Compile and monitor enrollment estimates for concepts and protocols in development, determine the feasibility of new studies, and provide reports to the Steering Committee and the Core Science Group;

Review draft protocols in conjunction with the protocol teams to identify implementation, recruitment, and retention issues;

Review protocol-specific case report forms in conjunction with the protocol teams for feasibility of implementation and recommend changes, as necessary;

Review protocol-specific consent forms to identify problem areas which might hinder patient understanding and/or IRB approval.

Assist in the development of education/training materials by:

Identifying the need for specific patient education and staff training;

Providing timely review to the TBTC collaborating centers for cultural sensitivity of education/training materials.

Monitor ongoing protocols:

In the early stages of open studies, and on an ad hoc basis, review implementation issues and develop strategies to address problem areas;

Work with protocol teams to regularly identify, evaluate, and monitor actual and potential problems/barriers to recruitment, accrual, and retention throughout the life of a protocol and recommend resolutions, and provide regular reports to the Steering Committee on accrual into ongoing protocols by unit;

Ensure maximum compliance in TBTC studies by developing compliance and retention strategies and assist in implementation of strategies at the unit level;

Review study closure plans for implementation issues;

Regularly review`summary data prepared by the Statistical Center for completeness and timeliness of data collection, eligibility errors, missed visits and loss to follow-up rates, data queries, and missed endpoints or

protocol violations identified by site monitors, and site monitoring reports;

Develop performance standards, evaluate whether or not they are being met, assess the scope of problems (system-wide versus individual units), and report findings and make recommendations to the Steering Committee;

Recommend methods to improve data quality;

Recommend reports to be generated by the Statistical Center related to quality assurance issues;

Assess and monitor unit capacity on an ongoing basis and report to the Steering Committee. Refine capacity assessment tools as needed;

Provide reports on TBTC quality assurance issues, by unit and by protocol, to the Steering Committee.

Generate original continuing quality improvement-related research and/or descriptive reports for publication or public presentation.

Membership of IQC:

A group of ten voting members will be responsible for carrying out the mission and functions of the IQC. Any TBTC member can apply for membership, and the Steering Committee will choose eight members from the slate of applicants who have submitted a brief description of their interest in and qualifications for membership (i.e., past and potential contributions to the mission and purpose of the TBTC). The other voting members are one representative each of the DTBE and the Monitoring Center. Non-voting members will include one representative each of the Data Center and the Core Science Group. (The representative of DTBE and of the Data Center may be the same person).

The IQC will set a standard for participation and report the standard to the Steering Committee. The IQC chair may request that a member who is not meeting the standard for participation resign from the committee and may request that a replacement be chosen either by special election or by special appointment.

A chair and co-chair of the IQC will be chosen by members.

Terms of office for the IQC members will be 2 years, and the terms will be staggered so that four members are elected one year and four the next year. Members can be re-elected.

Publications and Presentations (P & P) Committee

Mission: To encourage timely and accurate dissemination of the design, methods, and results of research performed by the TBTC; to ensure a high standard of scientific quality; to allow freedom for individual creativity; and to appropriately acknowledge the efforts of professional persons involved in the planning, conduct, and analysis of TBTC studies.

The P & P Committee will:

Ensure and expedite the orderly and timely presentation to clinicians, TB patients, and the scientific community of all pertinent data and conclusions resulting from TBTC studies;

Ensure that all scientific publications and presentations involving TBTC studies are accurate, scientifically sound, and consistent with the mission of the TBTC;

Ensure that all TBTC investigators and collaborating clinicians, professional and scientific support staff and DTBE staff have the opportunity to participate and be recognized in TBTC scientific publications and presentations, as appropriate;

Ensures that all scientific publications and presentations summarizing TBTC study results receive DTBE clearance/approval;

Maintain a record of P&P proposals as well as scientific publications and presentations.

Detailed information on P&P policies and procedures is attached as Appendix A.

P&P Committee Membership

The P&P Committee consists of 5 voting members, 4 of whom will be from the TBTC units, including a minimum of 3 Principal Investigators, confirmed by the TBTC Steering Committee. The other voting member will be a DTBE staff member appointed by the Co-Chair of the Steering Committee. Non-voting members include one representative from the TBTC Data Center.

Terms of membership and office shall be for 2 years on a rotating basis. For the four representatives from TBTC research units, nominations are solicited from the field as each position comes open. The nominations are submitted to the Steering Committee for voting or confirmation of nominees.

The representative from the TBTC Data Center may be reappointed.

The Chair and Co-Chair of the P&P Committee shall be selected from one of the TBTC representatives serving on the P&P Committee by a vote of the committee members. The Co-Chair will not automatically succeed the Chair; however, the Co-Chair may be nominated to run for the office of Chair.

Advocacy and External Relations Committee (AERC)

Mission: To promote the TBTC as an research organization contributing importantly to the goal of tuberculosis elimination.

The Advocacy and External Relations Committee will

Coordinate activities with other research organizations, including pharmaceutical and biologics companies;

Develop and implement an advocacy plan to promote recognition of the TBTC, especially among national decision makers;

Identify opportunities for obtaining financial support for TBTC activities;

Represent the TBTC externally and articulate the accomplishments of the TBTC to the larger research community.

Membership

The AERC consists of 5 voting members, 4 of whom will be from the TBTC units, including a minimum of 3 Principal Investigators, confirmed by the TBTC Steering Committee. The other voting member will be a DTBE staff member appointed by the Co-Chair of the Steering Committee

Terms of membership and office shall be for 2 years on a rotating basis. For the four representatives from TBTC research units, nominations are solicited from the field as each position comes open. The nominations are submitted to the Steering Committee for voting or confirmation of nominees.

The Chair and Co-Chair of the AERC shall be selected from one of the TBTC representatives serving on the AERC by a vote of the committee members. The Co-Chair will not automatically succeed the Chair; however, the Co-Chair may be nominated to run for the office of Chair.

Working Groups

Working Groups are long-term groups with specific objectives and tasks assigned by the Steering Committee or an Executive Committee. The performance of Working Groups require regular review by the parent Committee.

Working Groups will convene periodically, via conference calls and face-to-face meetings. The group will select a chair who will conduct the business of the group during conference calls and face-to-face meetings.

Recommendations from the Working Group will be presented to the parent Committee during periodic conference calls and face-to-face meetings. The recommendations will be discussed and voted upon prior to presentation to the Steering Committee for recommendations and/or approval. (If a Working Group reports directly to the Steering Committee, the Working Group will vote on recommendations prior to presentation to the Steering Committee.)

Working Groups which do not convene for at least 6 months will be dissolved.

Executive Affairs Group

The Executive Affairs Group is a Working Group of the Steering Committee that meets on a regular basis to implement Steering Committee decisions, oversee details of concept and protocol development and implementation following Steering Committee approval, identify problems in the day-to-day operation of the TBTC that may require the attention of the Steering Committee, provide whatever administrative support is required to accomplish Steering Committee goals, provide a forum for chairs of Executive Committees to discuss issues, and plan plenary sessions/speakers for TBTC group meetings.

The Executive Affairs Group will:

1. Assist in overseeing development of concepts and development and implementation of protocols.

2. Decide on the time frame for concepts and protocols to be submitted to units and DTBE for review.

3. Review summaries of comments from units and DTBE to ensure that they have been addressed by the protocol team.

4. Approve protocol team members recommended by the Core Science Group.

5. Assist in the evaluation of the progress of ongoing protocols.

6. Identify issues requiring the attention of the Steering Committee.

7. Plan TBTC group meetings.

8. With the assistance of the administrative Centers, provide general administrative support for the Steering Committee and the TBTC.

Executive Affairs Group membership:

Membership of the Executive Affairs Group includes: the Chair and Co-Chair of the Steering Committee, the Chairs of the Executive Committees, the Executive Coordinator of the Steering Committee, a representative of the Monitoring Center, and other DTBE staff as appropriate.

Task Forces

A Task Force is a short-term group with a specific objective assigned by the Steering Committee or and Executive Committee. It is anticipated that a Task Force will complete its assignment(s) within several months. Membership on a Task Force will be assigned by the parent Committee, based on interest, availability, and expertise in specific areas.

A facilitator will be selected who will conduct the business of the group during conference calls and face-to-face meetings, with the goal of completing assigned tasks as efficiently and quickly as possible.

Recommendations from the Task Force will be presented to the entire parent Committee membership during monthly conference calls and face-to-face meetings. The recommendations will be discussed and voted upon prior to presentation to the Steering Committee for recommendations and/or approval. Once the parent Committee members have agreed to accept the task force report and the Steering Committee has accepted the recommendation, the Task Force will be dissolved. (If a Task Force reports directly to the Steering Committee, the Task Force will vote on recommendations prior to presentation to the Steering Committee.)

6. Administrative Group

Coordinating Center (DTBE/REB).

The TBTC Coordinating Center will be based in the Research and Evaluation Branch, Division of TB Elimination, National Center for HIV, STD, and TB Prevention, CDC in

Atlanta GA. The Coordinating Center will provide administrative support to the TBTC. It will house CDC project officers for all TBTC studies, and will be responsible for tracking and confirmation of endpoint events and deaths in all TBTC protocols. Staff of the Coordinating Center will serve as liaison with the CDC Mycobacteriology Laboratory, and will be responsible for tracking the receipt of study isolates and the confirmation of susceptibility profiles. The Coordinating Center will represent CDC's interest in the TBTC to external agencies or institutions, such as the U.S. Food & Drug Administration and the National Institutes of Health. The Coordinating Center will serve also as liaison between the TBTC and the CDC Institutional Review Board; it will assure compliance of all TBTC sites with CDC IRB requirements, and will track approval of relevant consent forms. The Coordinating Center will store official versions of all TBTC documents, including protocols, consents, and data collection forms.

Data Center (DTBE/CSB & REB)

The TBTC Data Management Center will be based jointly in the Computing and Statistics Branch and the Research and Evaluation Branch, Division of TB Elimination, National Center for HIV, STD, and TB Prevention, CDC in Atlanta GA. Staff from both branches will participate in or oversee TBTC data activities which will include provision of statistical and epidemiologic study design expertise, design of data collection forms, randomization and enrollment of study patients, receipt of completed forms, data entry and verification, data cleaning, data analysis, provision of preliminary and final statistical analyses, and preparation and maintenance of master datasets for all TBTC protocols. The Data Center will be responsible for analyses prepared for DSMB meetings. The Data Center will store hard-copy of all completed data collection forms.

Monitoring & Support Center (WESTAT)

The TBTC Monitoring & Support Center (MSC) will be based in the offices of a contract research organization selected through an open competitive process. [The current holder of that contract is Westat, Inc. in Rockville MD.] The MSC will conduct semi-annual site monitoring visits at each of the clinical sites to evaluate site performance within TBTC protocols, to document data reported to the TBTC Data Center, to assure compliance with applicable FDA and IRB regulations, to provide relevant training or updates in study procedures, and to assist sites in their efforts to participate productively in the work of the consortium. The MSC will assist protocol teams and the Coordinating Center in the development of study forms and the definition of study procedures, the preparation of study documents such as procedure manuals, and the assurance of required logistics and supplies. In order to fulfill this responsibility, an appropriate representative of the MSC will participate on all protocol teams and in relevant Working Groups. The MSC will provide assistance in arranging, and will attend, all TBTC group meetings.

Financial Management Office (DTBE, CDC and appropriate other CDC fiscal offices)

Supervisory fiscal management for the TBTC will be the responsibility of fiscal and administrative staff in the Division of TB Elimination, in cooperation with the relevant other CDC fiscal offices. In managing individual contracts or agreements, CDC fiscal staff will relate to the appropriate fiscal officers at each of the non-Veterans Administration sites. In managing funds which support the VA sites, fiscal staff in DTBE will cooperate with administrative staff of the Washington D.C. VA Medical Center, who are responsible for management of funds transferred to the VA under the CDC-VA Memorandum of Agreement.

7. Review and Oversight

DTBE Scientific Advisory Group (SAG) will:

Provide the TBTC with the broad framework of DTBE research priorities and the role of TBTC research, particularly as it relates to other DTBE-sponsored research;

Communicate in a timely manner any substantive changes in DTBE priorities or plans for the TBTC;

Provide periodic review of the TBTC plan of work and of Steering Committee decisions based on merit, scientific mission, and priorities of DTBE;

Through the Associate Director for Science, DTBE, provide final approval of all TBTC research protocols and publications.

Membership on the SAG will consist of the DTBE Director, Associate Director for Science and Branch/Activity Chiefs, the Director of the NCID Division of Laboratory Research in TB/HIV/STD (or designee), and the Co-Chair of the TBTC Steering Committee.

The SAG will meet at least yearly. At these meetings, the Chair of the TBTC Steering Committee will present the current plan of work and recent decisions by the Steering Committee. When requested, other TBTC members, e.g., chairs of subcommittees or working groups, will give presentations to the SAG.

Data and Safety Monitoring Board (DSMB)

For each trial or study, an appropriately constituted DSMB should examine intermittently the endpoint and toxicity data, in order to make recommendations to the TBTC Steering Committee and to DTBE concerning continuation, termination

or other necessary modification of studies. These examinations should be based on the observed beneficial or adverse effects of the therapeutic or preventive interventions under study, should include a review of the general progress of the study, and should adhere to good scientific practice. The monitoring process can often be facilitated by early involvement of a DSMB in the design of studies, through the timely review of new protocols for studies to be monitored by the DSMB.

The DSMB will operative in accordance with guidelines established by CDC's National Center for HIV, STD and TB Prevention dated August 1996. Copies of the guidelines are available from the TBTC Coordinating Center.

CDC/Local Institutional Review Boards

All study protocols will be reviewed and approved by CDC's IRB, as well as by the local IRB's of each participating study site.

The primary role of the IRB is to protect the rights and welfare of human beings who are participants in the research. In accordance with the Federal Regulations an IRB may approve research only after it has determined that all of the following requirements are satisfied:

a. Risks to participants are minimized by using procedures that are consistent with sound research design, and that do not unnecessarily expose participants to risks, and whenever appropriate, researchers should employ procedures that are being performed on participants for prevention, diagnostic or treatment purposes.

b. Risks to participants are reasonable relative to anticipated benefits, if any, to participants, and the importance of the knowledge that may reasonably be expected to results from the research.

c. The selection of participants is equitable. In making this assessment the IRB must take into account the purposes of the research and the setting in which it will be conducted. The IRB must be particularly attentive to the special problems that may arise when research involves vulnerable populations, such as children, pregnant women, fetuses, prisoners, mentally disabled persons, economically or educationally disadvantaged persons. If any of the participants are likely to be susceptible to undue influence or coercion, the IRB may require additional safeguards in the study to protect such participants.

d. Informed consent will be sought from each prospective participant, or

the participant's legally authorized representative, generally by means of a written consent document. The IRB will carefully review these documents to assure that they contain the required elements of informed consent and that they are understandable to the study population.

e. The research plan makes adequate provisions for ensuring the safety of participants.

f. There are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data.

Once a study protocol has been approved by the TBTC Steering Committee, it will be submitted to the CDC IRB. Following approval at CDC, the protocol will be submitted for local review.

Study protocols which are continuing require yearly IRB re-review and approval by both CDC and local IRB's.

Additional and extraordinary review of study progress, changes in study protocols, and/or of other information of relevance to ongoing studies may be required as determined by the DSMB in consultation with the Chair and Co-Chair of the DTBE Steering Committee.

Advisory Council for the Elimination of Tuberculosis (ACET)

The role of ACET is to provide advice and recommendations regarding the elimination of tuberculosis to the Secretary of HHS, the Assistant Secretary for Health of HHS, and the Director of CDC. ACET makes recommendations regarding policies, strategies, objectives, and priorities; addresses the development and application of new technologies; and reviews the extent to which progress has been made in eliminating tuberculosis.

In this capacity, TBTC will request that ACET review the work plan and accomplishments of the TBTC at least yearly. Based on this review, ACET will make recommendations on current and future TBTC activities, helping ensure that the work of the TBTC is consistent with CDC's tuberculosis elimination strategy.

Appendix A

TUBERCULOSIS TRIALS CONSORTIUM
Publications and Presentations Committee
Policies and Procedures

Goals and Objectives

The goals and objectives of the Publications and Presentations Committee (P&P) are:

To assure timely publication and presentation in appropriate scientific venues of all relevant data and conclusions from TBTC studies.

To guarantee that all publications and presentations made on behalf of the TBTC are scientifically valid, are of the highest quality, and support the interests of the TBTC.

To assure that all investigators, study coordinators, CDC staff, and other persons receive appropriate credit for their work in TBTC-sponsored trials.

To allow CDC to exercise its review responsibility in a manner consistent with the overall mission of the TBTC.

To maintain a record of all TBTC scientific publications and presentations.

Membership

1. The P&P Committee consists of 5 voting members, 4 of whom will be from the TBTC units, confirmed by the TBTC Steering Committee. The other voting member will be a DTBE staff member appointed by the Co-Chair of the Steering Committee. Non-voting members include one representative from the TBTC Data Center.

2. Terms of membership and office shall be for 2 years on a rotating basis. For the four representatives from TBTC research units, nominations are solicited from the field as each position comes open. The nominations are submitted to the Steering Committee for voting or confirmation of nominees.

3. The representative from the TBTC Data Center may be reappointed.

4. The Chair and Co-Chair of the P&P Committee shall be selected from one of the TBTC representatives serving on the P&P Committee by a vote of the committee members. The Co-Chair will not automatically succeed the Chair; however, the Co-Chair may be nominated to run for the office of Chair.

Policies

Scientific Publications

There are several different types of scientific publications that may relate to TBTC work. These include, but are not limited to, original reports in peer-reviewed scientific

publications, review articles, book chapters, abstracts to be presented at scientific meetings, and other publications which present TBTC data. In general, the following types of manuscripts are those which are subject to the policies and procedures of the P&P Committee of the TBTC:

Original Reports

Primary manuscripts. A primary manuscript is one which presents the conduct of the trial and its main outcome(s). It is anticipated that there will be one primary manuscript from each TBTC protocol. These manuscripts will appear in peer-reviewed scientific publications.

Secondary manuscripts. Secondary manuscripts address scientific questions related to but outside the main study objectives of a TBTC trial, arise from data from more than one trial, or report analyses of samples collected in one or more trials. The publication of such secondary manuscripts should not jeopardize the completion of the parent study (or studies) or the publication of the primary manuscript. These manuscripts will appear in peer-reviewed scientific publications.

Abstracts. An abstract is a concise summary of the study design, methods, results, and/or interpretation of a trial or investigation which is to be presented at a scientific meeting in one of several formats (poster or oral presentation). Most abstracts are published but do not undergo the same rigorous peer review as manuscripts which appear in scientific journals.

Reviews

Review articles and book chapters do not contain original data which has not been previously published. They may however contain new syntheses of previously published material. Such manuscripts may fall under the purview of the P&P Committee if they are solicited on behalf of the TBTC or if they seek to represent the position of the TBTC on a particular topic or aspect of the consortium's work.

Review of papers and abstracts

The P&P Committee has responsibility for assuring that any abstract or manuscript presented on behalf of the TBTC contains accurate data which is clearly presented and correctly analyzed and interpreted. In addition, the P&P Committee will review authorship citations of all manuscripts to ensure that proper credit has been given for work performed.

Final drafts of abstracts and manuscripts must be reviewed and approved by the P&P Committee prior to submission for publication. In cases where a member of the P&P Committee is also an author of a manuscript, the Chairman of the Steering Committee

will appoint a member of the Executive Advisory Group to serve as an ad hoc reviewer for that paper. If necessary, the P&P Committee will consult members of the Steering Committee's Executive Advisory Group for advice on technical matters related to the manuscript.

Manuscripts will be reviewed by the CDC to ensure that they comply with CDC policies and procedures.

The P&P Committee will serve as the arbiter of any disputes arising regarding the content or authorship of manuscripts.

Authorship and Writing Group Membership

A writing group will be formed for each paper.

Primary manuscripts. The writing group will be chaired by the leader of the protocol team for each particular study, and that chair will determine the other members of the writing group. The writing group and authors should include those who have made significant contributions to the work represented by the manuscript. For publications dealing with major scientific questions of TBTC sponsored studies, members of the writing group should be drawn from the protocol team, but may also include other individuals who have contributed substantially to the protocol or its analysis. The chair of the writing group will serve as the first author for each manuscript, and the senior author for each manuscript will be the Tuberculosis Trials Consortium. Participating study sites and personnel and other study personnel not listed as authors will be listed in an appendix to the manuscript.

Secondary manuscripts. Preparation of secondary manuscripts follows the same procedure as for primary manuscripts except that the process may be initiated at different times during conduct or after closure of the study. After the secondary study has been approved by the Core Science Committee, the proposing investigator of a secondary study will establish and chair a writing committee, which may include other members of the proposing team of the secondary manuscript. The chair of the writing group will serve as the first author for each manuscript, and the senior author for each manuscript will be the Tuberculosis Trials Consortium. Participating study sites and personnel and other study personnel not listed as authors will be listed in an appendix to the manuscript.

Abstracts. Preparation of abstracts will follow the policies set forth for manuscripts, as above. There will be no appendix for abstracts.

No firm criteria exist for determining authorship. However, the following are statements from several leading medical journals regarding authorship:

The Lancet

"All persons designated as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content.

Authorship credit should be based only on substantial contributions to 1) conception and design, or analysis and interpretation of data; and to 2) drafting the article or revising it critically for important intellectual content; and on 3) final approval of the version to be published. Conditions 1, 2, and 3 must all be met. Participation solely in the acquisition of funding or the collection of data does not justify authorship. General supervision of the research group is not sufficient for authorship. Any part of an article critical to its main conclusions must be the responsibility of at least one author."

Annals of Internal Medicine

"Only those persons who contributed *directly* to the intellectual content of the paper should be listed as authors. Authors should meet *all* of the following criteria, thereby allowing persons named as authors to take public responsibility for the content of the paper.

1. Conceived and planned the work that led to the paper or interpreted the evidence it presents, or both.
2. Wrote the paper, or reviewed successive versions and took part in the revision process.
3. Approved the final version.

Holding positions of administrative leadership, contributing patients, and collecting and assembling data, however important to the research, are not, by themselves, criteria for authorship. Other persons who have made substantial, direct contributions to the work but cannot be considered authors should be acknowledged with their permission; description of their specific contributions is encouraged. The authors must also affirm that no other names of persons who contributed significantly to the work have been omitted from the acknowledgments.

To assist us in developing a system for identifying the roles of those who participated in the creation of a manuscript, the specific contributions of all authors, as well as those listed in the acknowledgments, should be listed in the appropriate section of the Authors' Form. We advocate publication of this information, but will only do so at the request of the authors."

The New England Journal of Medicine

“Large clinical trials from multiple institutions now involve dozens and sometimes hundreds of people in their conception, design, implementation, analysis, and preparation of reports for publication. Increasingly, we have become concerned about two interrelated aspects of many reports of multicenter studies: ambiguous authorship and lengthy acknowledgments.

Clear specification of authors is essential so that any substantive questions about a submitted or published study can be resolved. Authorship has been defined in many ways, but most of the definitions have in common a requirement that authors have sufficient intellectual involvement with the overall study to be able to take responsibility for it (1,2,3). Obviously, a clinician whose only contribution is to enter patients into a multicenter trial does not qualify for authorship, nor does a secretary in the trial office. Yet many such people may appear in a long list of members of a study group designated as the collective author of a study -- as a hypothetical example, the Boston Porphyria Study Group. In such a case, the study has at once too many authors, because not all of them could take comprehensive responsibility for the study, and too few, because it is not clear who is accountable. The problem is not limited to multicenter clinical trials, of course, but it is more likely in such studies because the cooperation of so many people is required and there is a tendency to offer authorship to obtain it.

A second problem is the growing length and detail of the acknowledgments. Traditionally, authors use acknowledgments to identify those who made special intellectual or technical contributions to a study that were not sufficient to qualify them for authorship. In reports of multicenter clinical trials, however, acknowledgments are often made to everyone who had anything to do with the study, including those who were merely carrying out their jobs, such as technicians. Sometimes principal investigators from each participating institution are acknowledged, even though they are also identified as authors. Many acknowledgments list committees, and the same person may be acknowledged several times on different committees.

We recently accepted a manuscript with an acknowledgment section that listed 63 institutions and 155 physicians, the number of patients each institution had contributed (some as few as one), the 51 members of seven different committees, their institutions and their specialties, and the secretaries in the trial office. Many persons were named on more than one committee. The paper was 12 pages long; the acknowledgments took up 5 pages. We do not consider an extensive and repetitious list of participants in a clinical trial, complete with committee assignments and other details of the trial's internal organization, a good use of Journal space; it cannot be of much interest to our readers. Furthermore, it tends to blur the distinction between authors and those who merely warrant acknowledgment. In the above example, all those who were acknowledged were also considered authors, because they were members of the group to which authorship was attributed.

The Journal subscribes to the criteria for authorship formulated by the International Committee of Medical Journal Editors and published in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals (4). According to these criteria,

> Each author should have participated sufficiently in the work to take public responsibility for the content. Authorship credit should be based only on substantial contributions to (a) conception and design, or analysis and interpretation of data; and to (b) drafting the article or revising it critically for important intellectual content; and on (c) final approval of the version to be published. Conditions (a), (b), and (c) must all be met.These guidelines were developed in part as a response to episodes of research fraud in which coauthors were too remote from the work or had too limited a role to exercise the responsibility that authorship implied (5).

Defining the criteria for an acknowledgment is, of course, far less important. We believe, however, that acknowledgments become less meaningful if they include people who were simply doing their jobs and who offered no unusual intellectual contribution or technical expertise to the endeavor.

In the past we dealt with concern about inappropriate authorship and acknowledgments on a case-by-case basis during the review process or after we accepted a manuscript for publication. But given the magnitude and frequency of the problems we are encountering and our concern that ad hoc decisions may appear arbitrary, we think it is appropriate to set out specific guidelines about authorship and acknowledgments. It is difficult to arrive at such guidelines because we do not wish to discourage cooperative research enterprises and we are aware that there are pressures on principal investigators to offer authorship as an incentive for enthusiastic cooperation. Yet it is not in our readers' interests to permit unlimited lists of authors and acknowledgments, and it undermines the meaning of authorship and the value of an acknowledgment.

Accordingly, we shall institute the following, fairly liberal guidelines for authorship and acknowledgments: (1) Authorship attributed only to a group (the Boston Porphyria Study Group) will not be acceptable. At least one person's name must accompany the group name. The group name should appear after the authors' names, as follows: "Thelma J. Smith, Louise J. Jones, and Duane J. Brown, for the Boston Porphyria Study Group." (2) If more than 12 authors are listed for a multicenter trial, or more than 8 for a study from a single institution, we shall require that each author sign a statement attesting that he or she fulfills the criteria for authorship of the Uniform Requirements. The reason for selecting these maximums, which are admittedly arbitrary, is that it is difficult to imagine that more than 12 people can have the comprehensive intellectual involvement necessary to fulfill the criteria for authorship. (3) We shall leave to the authors the choice of those acknowledged, but limit the space devoted to acknowledgments. To conserve space, those acknowledged will be listed only once, along with their institutions (one each). Committee names, numbers of patients contributed, and other details about the process of the trial will not be included. (4) If acknowledgments fill more than a column of Journal space (about 600 words of small type), we shall deposit them with the National Auxiliary Publications Service. At the authors' request we shall consider publishing fuller acknowledgments, including committee assignments, in reprints of the paper.

To remind authors of these guidelines, they will be included in our Information for Authors, which appears in the first issue of each month. We are aware that there may be individual circumstances in which these policies need to be modified. In particular, modifications may be required for reports of trials already in progress in which commitments have been made about the way participants are to be designated. Even in these cases, however, we would expect those named as authors to have fulfilled the criteria for authorship. We welcome your comments about these policies.”

Procedures

To implement the policies detailed above, the following procedures have been set forth:

A. Responsibilities of the writing committee

Designation of authorship: Before any manuscript/abstract is begun, a writing committee will be formed. The chair of the writing committee (under usual circumstances the protocol chair) will be the lead author of the manuscript, with other members of the committee and chain of authorship to be determined by the protocol chair according to the guidelines set forth above. In the case of a dispute regarding membership in a writing committee, the matter will be referred to the Publications and Presentations Committee for resolution according to the guidelines for authorship set forth above. Any such questions will be resolved by the P & P Committee within one week of referral. If a member of the P & P Committee is also one of the parties to the dispute, the chairman of the Steering Committee (or a person designated by the chairman) shall serve as an *ad hoc* member of the P & P Committee. The senior author for all manuscripts will be the Tuberculosis Trials Consortium. All articles will list all TBTC sites and key personnel in an appendix. The CDC will be listed as the funding source on all publications.

Notification to the P & P Committee of a planned manuscript: Upon formation of a writing group, the writing group chair shall notify the chair of the P & P Committee that a manuscript/abstract is in preparation. This notification shall include the tentative manuscript/abstract title as well as the authors of the paper in preparation, and should include the primary and secondary endpoints to be addressed in the report, as well as the analytic and statistical methods to be used.

Submission of manuscript/abstract to P & P Committee for review: Upon completion of the manuscript/abstract by the writing committee, it will be submitted to the P & P Committee for review.

Submission of manuscript for publication: Upon completion of review by the P & P Committee, the manuscript will be returned to the writing committee for submission to a journal for publication. The choice of journal to which the manuscript is to be submitted will be made by the writing committee.

Review of submitted manuscripts: The corresponding author for submitted manuscripts will be the first author of the paper, and this individual is responsible for responding to reviewer comments, handling negotiations concerning the manuscript, and communicating with the other co-authors

regarding the review process. The lead author will also notify the P & P Committee when a manuscript is submitted, and will inform the P & P Committee as to the status of the manuscript throughout the review process.

Responsibilities of the Publications and Presentations Committee

The Publications and Presentations Committee will maintain a record of all manuscripts/abstracts submitted or in preparation by members of the TBTC.

The P & P Committee will review all manuscripts and abstracts from the TBTC prior to submission for publication or presentation. This initial review will occur within 10 days of receipt for manuscripts and within 3 days of receipt for abstracts. Abstracts must be received by the P & P Committee no later than 14 days prior to the deadline for submission to a scientific meeting. Upon completion of the review, the P & P Committee will determine if the manuscript/abstract is acceptable for submission. If it is not, the manuscript will by returned to the writing committee with comments and will be re-reviewed after incorporation of suggestions of the P & P Committee. The review of the P & P Committee will be done in accordance with the policy objectives of the Committee and the TBTC, as set forth above. The major areas of interest of the P & P Committee in review are proper authorship credit and the accurate reporting and interpretation of data from TBTC studies. The P & P Committee reserves the right to review the original data for any manuscript and to request statistical review of the data if questions arise regarding the accurate reporting or interpretation of results.

The P & P Committee will maintain a bibliography of TBTC publications and presentations.

Appendix B: Management of Grants and Contracts from Outside Organizations

Studies and other activities of the TBTC may be supported through both direct financial and in-kind contributions from Outside Organizations, such as biologics and pharmaceutical companies and foundations and other charitable organizations which support biomedical research.

In most cases, proposals for provision of financial support and/or in-kind contributions from Outside Organizations will originate in one of two ways:

1) a member of the TBTC (including DTBE staff) will approach an Outside Organization for support related to a TBTC study which has been approved by the Steering Committee for protocol development (this would include studies which have progressed beyond this stage of development, e.g., ongoing studies)

2) an Outside Organization would approach a TBTC member proposing to support a TBTC study, either a study approved by the Steering Committee for protocol development or a proposed study which has not yet been reviewed/discussed by the Steering Committee

At the point when informal commitment has been made to provide outside support, the proposal will be reviewed by the Advocacy and External Relations Committee to ensure that the proposal is consistent with TBTC policy, is appropriate for the current TBTC program of work, and is coordinated with other outside collaboration. The AER will notify the Executive Affairs Group of these deliberations and recommendations.

Following review and approval by AER, the protocol chair assisted by the DTBE project officer assigned to the specific study, should solicit a draft contract or draft agreement from the Outside Organization. This should not occur before a concept has been approved by the Steering Committee for development.

When a formal contract is contemplated, the signatories will be

(1) the Outside Organization;

(2) an entity acting on behalf of the TBTC, designated the Recipient Organization. [Recipient Organizations include but are not limited to the TBTC Contract Research Organization, a Foundation affiliated with one of the TBTC sites, or another Foundation able to act on behalf of the TBTC (e.g, the CDC Foundation, the International Tuberculosis Foundation)];

(3) the DTBE project officer for the TBTC; and,

(4) the Chair or Co-Chair of the Steering Committee. The Chair or Co-Chair should not sign any agreements unless the Protocol Chair for the involved study has approved the final version of the document. In most cases, the Protocol Chair will be the individual interfacing with the Outside Organization on behalf of the TBTC. In general, individual investigators should not be signatories under their own names to TBTC contracts.

Draft contracts will be reviewed by the CDC Office of General Council (OGC), which on occasion may require modifications to comport with CDC requirements, and by the Recipient Organzation. The CDC OGC must approve amended drafts of contracts before any signatures are obtained. It is the responsibility of the CDC TBTC Project Officer to ensure that this approval is obtained. .

Funds will be disbursed by the Recipient Organization upon approval by the CDC TBTC Project Officer and (if appropriate) the project officer for the Recipient Organization. A procedure must be in place which documents the amounts and reasons for all disbursals of funds, thus allowing for reliable tracking of the use of TBTC contract funds. Funds from different contracts must not be co-mingled. It is the responsibility of the Recipient Organization to maintain a record of these transactions and to provide this record to the DTBE Project Officer when requested. The recipient organization may also have additional accounting responsibilities to the Outside Organization as specified in the contract.